December 18, 1998

Dr. Jane Henney
Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Henney:

We are writing to inquire into the facts underlying an article, "Fast-Track' Drug to Treat Diabetes Tied to 33 Deaths," published in the December 6 Los Angeles Times. The article cites the reservations of FDA review staff over the safety of Rezulin (troglitazone) prior to its approval and the increasing number of deaths and cases of liver damage associated with Rezulin.

These disclosures follow on the heels of a study recently published by the consumer health group Public Citizen, entitled "FDA Medical Officers Say Lower Standards Permit Dangerous Drug Approvals." The study raises serious concerns over whether new drugs have been approved against the judgement of agency reviewers, whether there is inappropriate pressure within the FDA to approve new drugs, and whether information is not being fully disclosed to FDA advisory committees by the agency.

In light of the similar concerns surrounding the approval of Rezulin, we would appreciate information regarding the following questions:

PATIENT DEATHS AND LIVER DAMAGE

1. How many deaths and cases of serious liver damage are attributable to, or associated with, Rezulin since its January 30, 1997 approval? How many have been reported directly to the FDA? How many were reported to the FDA by Rezulin's manufacturer, Warner-Lambert? Please provide the date of each report.

2. It is widely recognized that adverse reactions are underreported to the FDA through its MedWatch program and other postmarketing surveillance systems. Does the agency have an estimate of how significant this underreporting might be in the case of Rezulin?

3. Warner-Lambert's December 1 "Dear Doctor" letter downplays the disclosure of three new deaths from liver failure associated with Rezulin, stating, "You will be reassured to know that the additional reports received since early November do not indicate a greater frequency of liver injury or potential for serious harm than had been previously estimated."
Did the FDA approve or review this letter before its nationwide distribution? Does it concur with this assessment of Rezulin's safety, particularly in light of the labeling changes mandated by the agency?

4. Since January 30, 1997, the FDA has added a bold-face warning of Rezulin's danger of liver damage, and required three major changes in Rezulin's labeling. Each labeling change has called for increased testing of patient liver function. In light of the rising number of patient deaths and cases of liver damage, does the agency continue to believe that testing of liver function is an adequate means of preventing future fatalities and serious adverse reactions?

5. What proportion of patients are complying with the liver function tests mandated in Rezulin's revised labeling? Given the serious health risks to patients of noncompliance, are the FDA or Warner-Lambert monitoring such compliance? What steps are FDA and Warner-Lambert taking to ensure patient compliance?
DR. JOHN GUERIGUIAN

6. Why was Dr. John L. Gueriguian removed from the review of Rezulin?

7. Did Dr. Gueriguian recommend against the approval of Rezulin? Please provide copies of any memoranda, email, notes, or other documentation of Dr. Gueriguian's recommendations regarding Rezulin's safety, approval, or potential conditions of use.

8. What was the response of Dr. Gueriguian's superiors in the Division of Metabolic and Endocrine Drug Products (DMEDP) and Center for Drug Evaluation and Research (CDER) to such recommendations? Please provide copies of any memoranda, email, notes, or other documentation of such responses.

9. The Los Angeles Times describes a September 1996 meeting between DMEDP staff and representatives of Warner-Lambert, in which Dr. Gueriguian voiced reservations regarding Rezulin. Please provide any transcripts, memoranda, notes, or other documentation of this meeting and any subsequent communication from Warner-Lambert concerning this meeting.
REZULIN APPROVAL

10. Please provide any memoranda, email, notes or other documentation of concerns expressed by DMEDP staff prior to Rezulin's approval on January 30, 1997 regarding the product's potential risks of cardiovascular or liver damage.

11. On or prior to the December 11, 1996 meeting of the Endocrinologic & Metabolic Drugs Advisory Committee, did Dr. Solomon Sobel, Dr. Alexander Fleming, Dr. Robert Misbin or other DMEDP or CDER staff recommend to the committee members that regular liver function tests be a condition of Rezulin's approval? Did they recommend any other restrictions on the use of Rezulin as a condition of approval?

12. Please provide copies of any medical reviews of Rezulin written prior to December 11, 1996 for the use by the Endocrinologic & Metabolic Drugs Advisory Committee and any transcripts, memoranda, notes, or other documentation of the December 11 committee deliberations on Rezulin.

13. Rezulin was approved in the United Kingdom on July 31, 1997 and withdrawn from the market on December 1, 1997 after reports of six deaths and 130 cases of liver damage associated with Rezulin. Please provide copies of any memoranda, email, notes, or other documentation of the FDA's evaluation of the U.K.'s Medicines Control Agency decision to withdraw Rezulin from the market.

14. Did Dr. Richard Eastman, Director, Division of Diabetes, Endocrinology and Metabolism, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), have any communications with the Division of Metabolic and Endocrine Drug Products regarding the approval of Rezulin? Please provide copies of any memoranda, email, notes, or other documentation of any such communications.
We appreciate your time and attention to these issues, which we all recognize go to the heart of the public's confidence in the FDA. Recently, concerns have been raised over the adequacy of resources and statutory authorities available to the Food and Drug Administration (FDA) to ensure the safety or prescription drugs. In the past year alone, a record five new drugs have been removed from the market — as many recalls as there were in the previous decade.We hope you agree that it is in the agency's and the public's best interests that any doubts concerning the rigor and objectivity of the agency's approval of new drugs be addressed swiftly and conclusively.

Please contact us or have your staff contact John Ford of the Commerce Committee Minority staff at (202) 226-3400 or Paul Kim of Mr. Waxman's office at (202) 225-3976. We look forward to your response.

Sincerely,

JOHN D. DINGELL, Ranking Member, Committee on Commerce
SHERROD BROWN, Ranking Member, Subcommittee on Health and Environment
HENRY A. WAXMAN, Ranking Member, Committee on Government Reform and Oversight

Enclosure

cc: Congressman Tom Bliley
Congressman Mike Bilirakis